JMYT-314US

Appln. No.: 10/751,611

Amendment Dated June 24, 2005 Reply to Office Action of April 27, 2005

<u>Amendments to the Claims:</u> This listing of claims will replace all prior versions, and listings, of claims in the application

Listing of Claims:

- 1. (Canceled)
- 2. (Currently Amended) The process according to claim 491, wherein P is a tetrahydropyranyl (THP) protecting group.
- 3. (Currently Amended) The process according to claim 491 or claim 2, wherein X is iodine.
- 4. (Currently Amended) The process according to claim $\underline{491}$, wherein A is $(CH_2)_2Ph$, ----- represents a double bond, P is THP and X is I.
- 5.-7. (Canceled)
- 8. (Currently Amended) The process according to claim <u>55</u>7, wherein P is a tetrahydropyranyl (THP) protecting group.
- 9. (Currently Amended) The process according to claim <u>55</u>7, wherein A is $(CH_2)_2Ph$, ---- represents a double bond and P is THP.
- 10.-12. (Canceled)
- 13. (Currently Amended) The process according to claim <u>5812</u>, wherein P is a tetrahydropyranyl (THP) protecting group.
- 14. (Currently Amended) The process according to claim 5812, wherein A is $(CH_2)_2Ph$, ---- represents a double bond and P is THP.

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15.-17. (Canceled)

18. (Currently Amended) The process according to claim <u>61</u>17, wherein P is a tetrahydropyranyl

(THP) protecting group.

19. (Currently Amended) The process according to claim 6117 or claim 18, wherein A is

 $(CH_2)_2$ Ph and ---- represents a double bond.

20.-22. (Canceled)

23. (Currently Amended) The process according to claim 2264, wherein P is a tetrahydropyranyl

(THP) protecting group.

24. (Currently Amended) The process according to claim 2264, wherein A is (CH₂)₂Ph, P is

THP, --- represents a double bond, and compound (VIIa) reacts to give compound (VIa).

25. (Currently Amended) The process according to claim 2264, wherein A is (CH₂)₂Ph, P is

THP, represents a double bond, and compound (VIIb) reacts to give compound (VIb).

26. (Currently Amended) The process according to claim 2264, wherein A is (CH₂)₂Ph, ----

represents a double bond, and compound (VIIc) reacts to give compound (VIc).

27.-29. (Canceled)

30. (Currently Amended) The process according to claim 2967, wherein P is a tetrahydropyranyl

(THP) protecting group.

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31. (Currently Amended) The process according to claim 2967, wherein A is (CH₂)₂Ph, P is THP and compound (VIa) reacts to give compound (Va).

- 32. (Currently Amended) The process according to claim 2967, wherein A is (CH₂)₂Ph, P is THP and compound (VIb) reacts to give compound (Vb).
- 33. (Currently Amended) The process according to claim 2967, wherein A is (CH₂)₂Ph and compound (VIc) reacts to give compound (Vc).
- 34. (Canceled)
- 35. (Currently Amended) The process according to claim 3470, wherein P is a tetrahydropyranyl (THP) protecting group.
- 36. (Currently Amended) The process according to claim 3470, wherein A is $(CH_2)_2Ph$, P is THP, ---- represents a single bond, and compound (Va) reacts to give compound (IVa).
- 37. (Currently Amended) The process according to claim 3470, wherein A is (CH₂)₂Ph, P is THP, represents a single bond, and compound (Vb) reacts to give compound (IVb).
- 38. (Currently Amended) The process according to claim 3470, wherein A is $(CH_2)_2Ph$, ----- represents a single bond, and compound (Vc) reacts to give compound (IVc).
- 39.-40. (Canceled)
- 41. (Original) A process for synthesising Latanoprost comprising the steps of:
- a) preparing a compound of formula (3):

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said preparing comprising converting a compound of formula (1):

to a cuprate reagent and performing a 1,4 addition reaction between the cuprate reagent and a compound of formula (2):

b) selectively reducing the compound of formula (3) to provide a compound of formula (4):

c) dihydroxylating the compound of formula (4) to provide a compound of formula (7):

d) reducing the compound of formula (7) to provide a compound of formula (10):

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e) performing a diol cleavage reaction on the compound of formula (10) to provide a compound formula (13):

f) performing a Wittig reaction on the compound of formula (13) to provide a compound of formula (16):

g) esterifying the compound of formula (16) to provide a compound of formula (19):

h) deprotecting the compound of formula (19) to provide Latanoprost.

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42. (Currently Amended) A process for synthesising Latanoprost comprising the steps of:

a) preparing a compound of formula (3):

said preparing comprising converting a compound of formula (1):

to a cuprate reagent and performing a 1,4 addition reaction between the cuprate reagent and a compound of formula (2):

b) selectively reducing the compound of formula (3) to provide a compound of formula (4):

c) protecting the compound of formula (4) to provide a compound of formula (5):

d) dihydroxylating the compound of formula (5) to provide a compound of formula (8):

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reducing the compound of formula (8) to provide a compound of formula (11): e)

f) performing a diol cleavage reaction on the compound of formula (11) to provide a compound of formula (14):

performing a Witting-Wittig reaction on the compound of formula (14) to provide a g) compound of formula (17):

h) esterifying the compound of formula (17) to provide a compound of formula (20):

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- i) deprotecting the compound of formula (20) to provide Latanoprost.
- 43. (Original) A process for synthesising Latanoprost comprising the steps of:
- a) preparing a compound of formula (3):

said preparing comprising converting a compound of formula (1):

to a cuprate reagent and performing a 1,4 addition reaction between the cuprate reagent and a compound of formula (2):

b) selectively reducing the compound of formula (3) to provide a compound of formula (4):

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c) deprotecting the compound of formula (4) to provide a compound of formula (6):

d) dihydroxylating the compound of formula (6) to provide a compound of formula (9):

e) reducing the compound of formula (9) to provide a compound of formula (12):

f) performing a diol cleavage reaction on the compound of formula (12) to provide a compound of formula (15):

g) performing a Wittig reaction on the compound of formula (15) to provide a compound of formula (18):

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h) esterifying the compound of formula (18) to provide Latanoprost.

44.-48. (Canceled)

49. (New) A process for the preparation of a prostaglandin compound having the formula (I):

the process comprising a step of preparing a compound of formula (VIII):

wherein A is selected from the group consisting of C₁-C₆ alkyl groups; C₇-C₁₆ aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected

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from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; P is a hydroxyl protecting group; and ——— represents a double bond or a single bond; said step comprising converting a compound of formula (IX):

wherein A, P and ---- are as defined above and X is a leaving group, to a cuprate reagent and performing a 1,4 addition reaction between the cuprate reagent and a compound of formula (X):

wherein P is as defined above.

- 50. (New) The process according to claim 2, wherein the compound having the formula (I) is Travoprost.
- 51. (New) The process according to claim 49, wherein the compound having the formula (I) is Travoprost.
- 52. (New) The process according to claim 49, wherein A is CH₂CH₂-Ph, —— represents a double bond and P is THP, the process further comprising selectively reducing the compound of formula (VIII) to provide a compound of formula (4):

dihydroxylating the compound of formula (4) to provide a compound of formula (7):

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performing a diol cleavage reaction on the compound of formula (7) to provide a compound of formula (23):

performing a Wittig reaction on the compound of formula (23) to provide a compound of formula (26):

amidating the compound of formula (26) to provide a compound of formula (29):

deprotecting the compound of formula (29) to provide Bimatoprost.

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53. (New) The process according to claim 49, wherein A is CH₂CH₂-Ph, ----- represents a double bond and P is THP, the process further comprising selectively reducing the compound of formula (VIII) to provide a compound of formula (4):

protecting the compound of formula (4) to provide a compound of formula (5):

dihydroxylating the compound of formula (5) to provide a compound of formula (8):

performing a diol cleavage reaction on the compound of formula (8) to provide a compound of formula (24):

performing a Wittig reaction on the compound of formula (24) to provide a compound of formula (27):

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amidating the compound of formula (27) to provide a compound of formula (30):

deprotecting the compound of formula (30) to provide Bimatoprost.

54. (New) The process according to claim 49, wherein A is CH₂CH₂-Ph, ----- represents a double bond and P is THP, the process further comprising selectively reducing the compound of formula (VIII) to provide a compound of formula (4):

deprotecting the compound of formula (4) to provide a compound of formula (6):

dihydroxylating the compound of formula (6) to provide a compound of formula (9):

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performing a diol cleavage on the compound of formula (9) to provide a compound of formula (25):

performing a Wittig reaction on the compound of formula (25) to provide a compound of formula (28):

HO
$$Ph$$
 OH (28)

amidating the compound of formula (28) to provide Bimatoprost.

55. (New) A process for the preparation of a prostaglandin compound having the formula (I):

wherein A is selected from the group consisting of C₁-C₆ alkyl groups; C₇-C₁₆ aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected

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from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; B is selected from OR'' and NHR'' wherein R'' is C_1 - C_6 alkyl groups; and \longrightarrow represents a double bond or a single bond;

the process comprising a step of preparing a compound of formula (VIIa):

wherein A, P and ---- are as defined above.

- 56. (New) The process according to claim 8, wherein the compound having the formula (I) is Travoprost.
- 57. (New) The process according to claim 55, wherein the compound having the formula (I) is Travoprost.

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58. (New) A process for the preparation of a prostaglandin compound having the formula (I):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; B is selected from OR'' and NHR'' wherein R'' is C_1 - C_6 alkyl groups; and $\xrightarrow{----}$ represents a double bond or a single bond;

the process comprising a step of preparing a compound of formula (VIIb):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; P is a hydroxyl protecting group and $\xrightarrow{----}$ represents a double bond or a single bond; said step comprising protecting a compound of formula (VIIa):

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wherein A, P and are as defined above, with a hydroxyl protecting group.

- 59. (New) The process according to claim 13, wherein the compound having the formula (I) is Travoprost.
- 60. (New) The process according to claim 58, wherein the compound having the formula (I) is Travoprost.
- 61. (New) A process for the preparation of a prostaglandin compound having the formula (I):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; B is selected from OR'' and NHR'' wherein R'' is C_1 - C_6 alkyl groups; and $\xrightarrow{----}$ represents a double bond or a single bond;

the process comprising a step of preparing a compound of formula (VIIc):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with

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one to three substituents selected from the group consisting of C₁-C₆ alkyl groups, halo and CF₃ and ---- represents a double bond or a single bond; said step comprising deprotecting a compound of formula (VIIa):

wherein A and ---- are as defined above and P is a protecting group.

- 62. (New) The process according to claim 18, wherein the compound having the formula (I) is Travoprost.
- 63. (New) The process according to claim 61, wherein the compound having the formula (I) is Travoprost.
- 64. (New) A process for the preparation of a prostaglandin compound having the formula (I):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; B is selected from OR" and NHR" wherein R" is C_1 - C_6 alkyl groups; and ______ represents a double bond or a single bond;

the process comprising a step of preparing a compound of formula (VIa), (VIb), (VIc), (Va), (Vb) or (Vc):

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wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and P is a hydroxyl protecting group;

said step comprising dihydroxylating a compound of formula (VIIa), a compound of formula (VIIb) or a compound of formula (VIIc):

wherein A and P are as defined above and ---- is a double or single bond.

- 65. (New) The process according to claim 23, wherein the compound having the formula (I) is Travoprost.
- 66. (New) The process according to claim 64, wherein the compound having the formula (I) is Travoprost.

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67. (New) A process for the preparation of a prostaglandin compound having the formula (I):

the process comprising a step of preparing a compound of formula (Va), (Vb) or (Vc):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and P is a hydroxyl protecting group;

said step comprising reducing a double bond of a compound of formula (VIa), a compound of formula (VIb) or a compound of formula (VIc):

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wherein A and P are as defined above.

- 68. (New) The process according to claim 30, wherein the compound having the formula (I) is Travoprost.
- 69. (New) The process according to claim 67, wherein the compound having the formula (I) is Travoprost.
- 70. (New) A process for the preparation of a prostaglandin compound having the formula (I):

wherein A is selected from the group consisting of C_1 - C_6 alkyl groups; C_7 - C_{16} aralkyl groups wherein an aryl portion thereof is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; and $(CH_2)_nOR'$ wherein n is an integer from 1 to 3 and R' represents a C_6 - C_{10} aryl group which is unsubstituted or substituted with one to three substituents selected from the group consisting of C_1 - C_6 alkyl groups, halo and CF_3 ; B is selected from OR'' and NHR'' wherein R'' is C_1 - C_6 alkyl groups; and $\xrightarrow{----}$ represents a double bond or a single bond;

the process comprising a step of preparing a compound of formula (IVa), (IVb) or (IVc):

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wherein A and P are as defined above.

71. (New) The process according to claim 35, wherein the compound having the formula (I) is Travoprost.

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72. (New) The process according to claim 70, wherein the compound having the formula (I) is Travoprost.